REMARKS

In the subject Office Action, the Examiner rejected claims 22-27 under 35 U.S.C. § 101 and the first paragraph of Section 112 for lack of utility and enablement. The Examiner also rejected claims 22 and 27 under the second paragraph of 35 U.S.C. § 112 as being indefinite. The Examiner maintained and held in abeyance the priority determination. Lastly, the Examiner maintained the rejection of claims 22-27 under 35 U.S.C. § 102 as being anticipated by Holtzman et al.

Applicants respectfully traverse the rejections and request that the Examiner consider the following remarks in response to the Office Action.

Claim 27 has been cancelled. Claim 22 has been amended to clarify that the claimed antibody specifically binds the polypeptide of SEQ ID NO:69. Support for amendment of claim 22 may be found throughout the specification, including on page 16, lines 1-3. Claims 22-26 are now pending.

Priority Determination:

Applicants note that in the Office Action dated March 12, 2003, the Examiner agreed to delay the determination of priority until after the utility rejection is fully resolved. Applicants believe that they have resolved this utility issue and therefore direct the Examiner's attention to the arguments made herein, previous Applicant's arguments submitted on January 30, 2003, and the Goddard Declaration, also filed January 30, 2003. Applicants submit that this evidence demonstrates that Applicants are entitled to priority of at least December 17, 1997 **(correct?).** Therefore, Applicants request reconsideration of the determination of priority in view of the submission of all the evidence showing utility of the claimed invention.

Rejection of Claims Under 35 U.S.C. § 101 and 112, First Paragraph, Lack of Utility and Enablement:

The Examiner has rejected claims 22-27 under both 35 U.S.C. § 101 and 112, first paragraph, as being drawn to an invention that lacks utility. More specifically, the Examiner stated that the invention is not supported by either a credible, specific and substantial utility or a well established utility. Furthermore, the Examiner indicated that the Goddard Declaration, filed under CFR 132 on January 30, 2003, is insufficient to overcome the rejection because, even though it demonstrates that the increase of the DNA levels of certain markers may be indicative of cancer, the Declaration does not address how the DNA levels relate to the protein expression levels. In fact, the Examiner argues that an increase in the mRNA level expression does not necessarily result in an increased protein expression levels. Applicants respectfully request reconsideration of the rejection of claims 22-27, 30, 31, 33, and 34 for the reasons discussed below.

Applicants respectfully direct the Examiner's attention to several publications and abstracts of publications that demonstrate that mRNA levels correlate with protein expression levels, attached hereto as Appendix A. These publications make it clear that skilled artisans recognize that the expression levels of mRNA often correlate with the protein expression levels. For example, Maruyama *et al.* (Am. J. of Pathol., Sept. 1999, Vol. 155, No. 3, pgs. 815-822) showed a correlation between mRNA levels and protein levels of three of the helix-loop-helix proteins, Id-1, Id-2, and Id-3. According to Maruyama *et al.*, the mRNA and protein levels of all three species were increased in pancreatic cancer tissues as compared to the normal or chronic pancreatitis control tissues. Also, Ginestier *et al.* (Am. J. Pathol., Oct. 2002, 161(4):1223-33) demonstrated a correlation between cDNA (cDNA array analysis) and protein expression levels (using tumor tissue microarray analysis) in one-third of the examined molecules with proven or suspected role in breast cancer.

Applicants also include several other publications for the Examiner's consideration. For example, Dalifard *et al.* (Int. J. Mol. Med., May 1998, 1(5):855-61) showed that in breast cancer, a correlation (r=0.85) existed between c-erbB2 (oncogene encoding for

p185 protein) expression (as determined by Southern blot method) and p185 protein expression levels (as determined by immunoenzymetric assay). Also, Hareuveni *et al.* (Eur. J. Biochem., May 1990, 189(3): 475-86) found a correlation between expressed tumor antigen species with the allelic forms as well as significantly increased protein expression in breast cancer. Furthermore, Barr *et al.* (J. Parasitol., April 2003, 89(2):381-4) demonstrated that in a canine model of Chagas disease, mRNA levels (as determined by Northern blotting) and protein expression levels (as determined by Western blotting) of the plasma membrane calcium pump (PMCA) were increased in cardiac tissue by 77% and 58%, respectively, as compared to normal controls.

Accordingly, because the RNA levels and the protein expression levels have been found to correlate in different types of cancers as well as other diseases, Applicants assert that it is reasonable to expect the protein levels of the polypeptide encoded by the SEQ ID NO: 69 to be increased in cancer tissue. The increase in protein levels can then be detected by the antibodies of this invention.

Considering these remarks, Applicants respectfully assert that the claimed invention has utility and is fully enabled. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejections under § 101 and the first paragraph of § 112.

Rejection of Claims Under 35 USC § 112, Second Paragraph - Indefiniteness:

The Examiner rejected claims 22 and 27 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner acknowledges that the difference between claims 22 and 27 is the use of the terms "binds" and "specifically binds," respectively. However, the Examiner asserts that the specification does not define these terms and that Applicants do not support their contention that a skilled artisan would recognize the definitions submitted by the Applicants. Applicants

respectfully disagree. Claim 22 now recites "an antibody that specifically binds to the polypeptide shown in Figure 26 (SEQ ID NO:69)," and claim 27 has been cancelled. Therefore, the rejection is moot. Applicants maintain that one skilled in the art would recognize the definition of "specifically binds," which is also found throughout the specification, including on page 16, lines 1-3. Accordingly, Applicants request that the Examiner's rejection of claims 22 and 27 under § 112, second paragraph be withdrawn.

Rejection of Claims Under 35 USC § 102 Anticipation:

Claims 22-27 remain rejected under 35 U.S.C. § 102(a) and (e) as being anticipated by U.S. Patent Number 6,225,085 (Holtzman *et al.*).

The Examiner notes that Holtzman *et al.* disclose a polypeptide, LRSG, which is 98.4% identical to the SEQ ID NO: 69 of the instant application. The Examiner notes that although Holtzman *et al.* disclose LRSG, which differs from SEQ ID NO: 69 of the present application by 75 residues, "at 598 out of 673 [amino acids], the two proteins are absolutely identical."

Applicants submit that SEQ ID NO: 69 of Applicants invention is not identical to the sequence disclosed in Holtzman *et al.* and therefore claims 22-27 are not anticipated. According to the MPEP § 2131, "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The *identical* invention must be shown in as complete detail as is contained in the ... claim." *Id.* Also, *see* MPEP § 2131; *Verdegaal Bros. v. Union Oil Co. of CA*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants submit that two amino acid sequences that differ by 75 amino acids are not identical.

The Examiner indicated that the sequence differences existing between the polypeptide of this invention and the polypeptide sequence according to Holtzman *et al.*

do not correspond to major structural features that would affect the folding as well the ability of antibodies to bind to these polypeptides, specifically or otherwise. However, Applicants direct the Examiner attention to a review by Bowie *et al.* (Science, March 1990, 247:1306-1310) illustrating several examples of how a single amino acid substitution in a polypeptide sequence has significant structural and functional consequences. To carry out their function, proteins require the binding residues or the catalytic residues to be precisely oriented in three dimensions (Bowie *et al.*, Science, March 1990, 247:1306-1310). Therefore, due to the differences of 75 residues in two amino acid sequences, these two amino acid sequences likely encode two different, *i.e.* not identical polypeptides.

More specifically, as previously noted, the polypeptide described by Holtzman *et al.* contains an additional 75 residues not present in the DNA44804 polypeptide of the present invention. Applicants respectfully point out that this deletion of 75 residues from the polypeptide of this invention will have significant effects on the structure, stability and unfolding-refolding of the polypeptide. For example, Chaudhuri *et al.* (J. Mol. Biol. 1999, 285(3):1179-94) have shown that although the overall structure of the two proteins, the native and recombinant proteins, might be the same, the extra methionine residue at the N terminus of the recombinant protein remarkably affected the native-state stability and electric properties. According to Chaudhuri *et al.*, the protein with one less residue was more stable, was less negatively charged and unfolded faster then the protein with the additional residue. This author concluded that the difference in one residue resulted in electrostatic interactions and destabilization of the protein containing the additional residue through a conformational entropy effect. Based on these findings, Applicants submit that the deletion of 75 amino acids would have significant consequences on the structure, stability and the ability of the polypeptide to bind to the antibodies of this invention. As a result, it is clear that the polypeptide taught by Holtzman *et al.* does not anticipate the claimed invention. Accordingly, the Holtzman *et al.* reference is not a proper anticipatory reference of any currently pending claims. The Applicants respectfully request that the Examiner reconsider and withdraw this rejection of the claims.

The Applicants respectfully assert that the application is now in condition for allowance and request a timely notice of allowance be issued in this case. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned.

Applicants believe no fee is due in connection with the filing of this Amendment, however, should any fees be deemed necessary for any reason relating to this paper, the Commissioner is hereby authorized to deduct said fees from Brinks Hofer Gilson & Lione Deposit Account No. 23-1925. a duplicate copy of this document is enclosed.

Respectfully submitted,

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